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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Process for the preparation of tocopheryl acetate

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Process for the preparation of tocopheryl acetate

The present invention relates to a novel process for the preparation of tocopheryl acetate. Industrial syntheses of vitamin E, α-tocopherol, are based on the reaction of 2,3,5-trimethylhydroquinone with isophytol or phytyl halides, see Ullmann's Encyclopedia of Industrial Chemistry Vol. A27, VCH (1996), pp. 478-488. Since α-tocopherol is labile against oxidative conditions, it is usually converted into its acetate which is more stable and more convenient to handle. Thus, the manufacture of the usual commercial form of vitamin E, viz., tocopheryl acetate, involves the additional step of esterifying α-tocopherol (as obtained by the reaction of of 2,3,5-trimethylhydroquinone with isophytol or phytyl halides). 2,3,5-trimethylhydroquinone, in turn, is obtained from ketoisophorone via 2,3,5-trimethylhydroquinone diacetate and saponification of the latter. The present invention provides a new approach to tocopheryl acetate. According to that approach, 2,3,6-trimethylhydroquinone-1-acetate is reacted with either isophytol or phytol to produce tocopheryl acetate or 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate, whereupon the latter is submitted to ring closure to obtain tocopheryl acetate.

While the preparation of (all-rac)-α-tocopheryl acetate is preferred the invention is not limited to the preparation of that particular steric form and other steric forms can be obtained by using a phytyl starting material which has the appropriate stereoconformation. Thus, (RS,R,R)-α-tocopheryl acetate will be obtained when using (R,R)-phytol, (R,R,R)-isophytol, or (S,R,R)- isophytol or (RS,R,R)- isophytol.

Thus, in a first aspect, the present invention relates to a process which comprises reacting 2,3,6-trimethylhydroquinone-1-acetate with isophytol or phytol in an aprotic organic solvent in the presence of a catalyst of the formula $M(RSO_3)_n$, wherein M is a silver,

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gallium or rare earth metal cation, n is the valence of the cation M, and R is fluoro, fluorinated lower alkyl or fluorinated aryl, to produce α-tocopheryl acetate.

In another aspect, the invention relates to a process which comprises reacting 2,3,6-trimethylhydroquinone-1-acetate with isophytol or phytol in the presence of a catalyst of the formula $M(RSO_3)_n$, wherein M, n and R are as defined above, to produce 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate and/or an isomer thereof and cyclizing the 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate or an isomer thereof obtained to produce α-tocopheryl acetate.

Examples of rare earth metal cations which may be present in the catalyst for use in the present invention are Sc^{3+}, Ga^{3+}, Y^{3+}, Lu^{3+}, Hf^{4+}, La^{3+}, Ho^{3+}, Tm^{3+}, and Yb^{3+}. Preferred cations are Ag^{+}, Cu^{+}, Ga^{3+}, Sc^{3+}, Lu^{3+}, Hf^{4+}, Ho^{3+}, Tm^{3+}, Yb^{3+}, and especially Sc^{3+}.

The reaction in accordance with the present invention is suitably carried out in the presence of a solvent or solvent mixture such as conventionally used in Friedel-Crafts reactions. Examples of such solvents are aprotic organic solvents, especially aliphatic hydrocarbons, e.g., heptane, hexane, cyclohexane, methylcyclohexane and octane, and aromatic hydrocarbons, e.g. benzene, toluene and the xylenes. Preferred are two phase solvent mixtures comprising polar and apolar solvents. Examples of polar solvents in such two phase solvent mixtures are aliphatic and cyclic ketones, such as diethyl ketone, isobutyl methyl ketone, cyclopentanone and isophorone; aliphatic and cyclic esters and lactones, such as ethyl acetate, isopropyl acetate, and γ-butyrolactone; and carbonates such as ethylene carbonate and propylene carbonate or mixtures thereof. Examples of apolar solvents in such two phase solvent mixtures are aliphatic and aromatic hydrocarbons as specified above, particularly aliphatic hydrocarbons. Preferred two phase solvent mixtures are mixtures of ethylene carbonate or propylene carbonate and hexane, heptane or octane, especially ethylene carbonate and heptane (e.g., of about 1 : 1 by vol.).

The catalyst may be present in an amount of from about 0.001 mol-% to about 1 mol-%, preferably in an amount of about 0.05 to about 0.1 mol-%, based on phytol or isophytol, respectively. Suitably, the reaction temperature for the alkylation is 293 K to 433 K, preferred are 353 K to 423 K, and most preferred 373 K to 400 K.

The conversion of 2,3,6-trimethylhydroquinone-1-acetate to tocopheryl acetate by the process of this invention may proceed in one step or may be carried out with isolation of an intermediate, 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate. Further, isomers of the latter, viz., (*Z*)- or(*E*)- acetic acid 4-hydroxy-2,5,6-trimethyl-3-(3,7,11,15-tetramethyl-

hexadec-3-enyl)-phenyl ester and/or acetic acid 4-hydroxy-2,5,6-trimethyl-3-[3-(4, 8,12-trimethyl-tridecyl)-but-3-enyl]phenyl ester may be formed in minor amounts in the reaction mixture. All these intermediates may be cyclized by heating to yield the desired product, tocopheryl acetate. The cyclization may be carried out using the same catalysts and reaction conditions as those used in the alkylation.

The starting 2,3,6-trimethylhydroquinone-1-acetate may be obtained, e.g., by selective hydrolysis of 2,3,5-trimethylhydroquinone-diacetate as described in EP 1 239 045.

The following Examples illustrate the invention further.

Example 1

In a four-necked flask equipped with stirrer, water separator, and reflux condenser, 19.7 g (100 mmol) of trimethylhydroquinone-1-monoacetate and 25 ml of solvent (toluene, n-butyl acetate or heptane) were heated with stirring under argon atmosphere to reflux temperature (oil bath 413-418 K). After the addition of catalyst (see Table 1 below), 36.18 ml (100 mmol) of isophytol were added at a rate of 0.8 ml/min. The reaction mixture was heated under reflux for 30 min after completion of the addition of the isophytol. The reaction mixture was cooled and evaporated under reduced pressure. A viscous oil was obtained. For the yield of (all-*rac*)-α-tocopheryl acetate see Table 1.

Table 1

Catalyst	mol% [1]	Solvent	% A	% B	% C	% D
AgOTf	0.01	Toluene	11.1	55.4	0	24.1
$Sc(OTf)_3$	0.05	Toluene	6.2	64.6	0.2	22.9
$Hf(OTf)_4$	0.005	Toluene	19.4	47.8	0.2	26.1
$Ga(OTf)_3$	0.01	Toluene	0.1	71.6	0.8	20.8
AgOTf	0.01	Buac	0.3	62.4	0.4	27.4
$Sc(OTf)_3$	0.05	Buac	7.7	53.8	0.3	30.2
$Hf(OTf)_4$	0.005	Buac	1.6	60.7	0.6	29.3

$Ga(OTf)_3$	0.01	Buac	0.8	59.2	1.2	31.0
$Hf(OTf)_4$	0.005	Heptane	19.6	54.1	0	20.1

[1] based on isophytol   Buac : n-butyl acetate

A : 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate (and minor amounts of isomers)

B : (all-rac)-α-tocopheryl acetate

C : (all-rac)-α-tocopherol

D : "phytadienes" (a mixture of several C-20 isomers formed by dehydration reactions of starting material)

Example 2

In a four-necked flask equipped with stirrer, water separator, and reflux condenser, 19.7 g (100 mmol) of trimethylhydroquinone-1-monoacetate and 25 ml of γ-butyrolactone were heated with stirring under argon atmosphere to approx. 383 K (oil bath 388 K). After the addition of catalyst (see Table 2), 36.18 ml (100 mmol) of isophytol were added at a rate of 0.8 ml/min. The reaction mixture was heated under reflux for 30 min after completion of the addition of the isophytol. The reaction mixture was cooled to 353 K and extracted three times with 50 ml of heptane. The combined heptane phases were evaporated under reduced pressure. A viscous oil was obtained. For the yield of (all-*rac*)-α-tocopheryl acetate see Table 2.

Table 2

Catalyst	mol% [1]	% A	% B	% C	% D
AgOTf	0.01	50.6	2.0	0	23.6
$Sc(OTf)_3$	0.05	37.4	18.5	0.2	24.9
$Hf(OTf)_4$	0.005	46.0	6.5	0	22.4
$Ga(OTf)_3$	0.01	41.3	9.4	0	24.6

[1] based on isophytol

A : 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate (and minor amounts of isomers)

B : (all-rac)-α-tocopheryl acetate

C : (all-rac)-α-tocopherol

D :"phytadienes"

Example 3

In a four-necked flask equipped with stirrer, water separator, and a reflux condenser, 39.24 g (200 mmol) of trimethylhydroquinone-1-monoacetate, 30 g of ethylene carbonate and 450 ml of heptane were heated with stirring under argon atmosphere to reflux (oil bath 413 K). After the addition of catalyst (see Table 3), 36.18 ml (100 mmol) of isophytol were added at a rate of 0.8 ml/min. The reaction mixture was heated for additional 10 min., then the heptane was distilled off within approx. 20 min. Afterwards the reaction mixture was heated for the time indicated in table 3, i. e. 25 min, at 353-363 K. The reaction mixture was cooled down to 353 K. 150 ml heptane were added to the carbonate phase. The reaction mixture was stirred for additional 10 min at 353-363 K. The mechanical stirrer was removed and the reaction mixture was cooled to 278 K. The heptane layer was separated and evaporated under reduced pressure. A viscous oil was obtained. For the yield of (all-*rac*)-α-tocopheryl acetate see Table 3

Table 3

Catalyst	mol% [1]	Reaction time (min) [2]	% A	% B	% C	% D
$Sc(OTf)_3$	0.0125	60	1.6	90.7	0.5	3.5
$Sc(OTf)_3$	0.0125	75	0.6	92.1	0.6	3.3
$Sc(OTf)_3$	0.05	25	0	92.3	2.5	3.2
AgOTf	0.05	25	0	82.9	12.2	2.6
AgOTf	0.01	25	6.1	87.0	0.3	3.9
AgOTf	0.01	60	0	93.0	2.1	2.5
$Hf(OTf)_4$	0.005	60	0.2	93.3	1.4	3.0
$Ga(OTf)_3$	0.05	25	0	78.7	16.1	1.7
$Ga(OTf)_3$	0.01	25	0	92.2	2.1	3.2

[1] based on isophytol [2] after heptane was distilled off

A : 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate (and minor amounts of isomers)

B : (all-rac)-α-tocopheryl acetate

C : (all-rac)-α-tocopherol

D : "phytadienes"

Example 4

In a four-necked flask equipped with stirrer, water separator, and reflux condenser, 39.24 g (200 mmol) of 2,3,6-trimethylhydroquinone-1-monoacetate, 30 g of ethylene carbonate, and 450 ml of heptane were heated under argon atmosphere to reflux (oil bath 140°C). After the addition of catalyst (see Table 4 below), 36.18 ml (100 mmol) of isophytol were added at a rate as indicated in table 4, i. e. of 0.8 ml/min. Approx. 1.8 ml water were separated after complete addition of the isophytol. Afterwards the reaction mixture was heated for 10 min under reflux. Stirring was discontinued and the reaction mixture cooled to 5°C. The heptane layer was separated and evaporated under reduced pressure. A viscous oil was obtained. For the yield of *(E,Z)*-(all-*rac*)-3-phytyl-2,5,6-trimethylhydroquinone-1-monoacetate (6) (*E:Z* = 2.2-2.4:1) see Table 4

Table 4:

Catalyst	mol% [1]	IP feed [2]	% A	% B	% C	% D	% E
$Sc(OTf)_3$	0.05	0.8	55.6	33.4	1.3	6.4	0
$Sc(OTf)_3$	0.01	0.8	72.5	1.9	0	4.8	12.1
$Sc(OTf)_3$	0.01	0.4	85.9	2.6	0	5.7	0
$Ga(OTf)_3$	0.0075	0.8	69.0	20.2	0.4	5.9	0

[1] based on isophytol [2] (ml/min)

A : 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate (and minor amounts of isomers)

B : (all-rac)-α-tocopheryl acetate

C : (all-rac)-α-tocopherol

D : "phytadienes"

E : isophytol

Example 5

1.00 mmol of (*E/Z*)-(all-*rac*)-3-phytyl-2,5,6-trimethylhydroquinone-1-monoacetate was transferred to a Schlenk tube under argon and dissolved in 3 ml of solvent (for ethylene carbonate, 1.2 g). The solution was heated up to 353 to 363 K (oil bath temperature) and 25 µl (0.05 mol%) or 12.5 µl (0.025 mol%) of a stock solution of the catalyst in water (for $Sc(OTf)_3$ 0.2 molar; $Ga(OTf)_3$ 0.2 molar; AgOTf 0.2 molar; $Hf(OTf)_4$ 0.2 molar) were added. Then the solution was cooled to room temperature and the solvent removed under reduced pressure (in the case of toluene and *n*-butyl acetate). In the case of γ-butyrolactone the reaction mixture was extracted three times with approx. 5 ml heptane. For the ethylene carbonate system, 5 ml heptane were added, the mixture was cooled down to 278 K, the layers were separated, and the heptane phase was concentrated in vacuo. The obtained oils were examined by GC analysis. For the yields see table 5.

Table 5

Catalyst	mol% [1)]	K [2)]	Solvent	% A	% B	% C	% D
$Sc(OTf)_3$	0.05	403	EC	6.0	94.9	0.1	0.9
$Sc(OTf)_3$	0.05	413	EC	0.1	99.4	1.3	0.9
$Sc(OTf)_3$	0.05	403	γ-bulac.	0.1	100.7	1.0	1.2
$Sc(OTf)_3$	0.05	403	Buac	85.8	5.7	0	4.7
$Sc(OTf)_3$	0.05	403	Toluene	63.5	39.0	0	1.0
$Ga(OTf)_3$	0.05	413	EC	0	92.6	10.1	0.6
AgOTf	0.05	413	EC	6.0	94.8	0.3	0.9
$Hf(OTf)_4$	0.05	413	EC	0	86.6	16.1	0.7
$Ga(OTf)_3$	0.025	413	γ-bulac.	0	98.9	3	0.9
$Hf(OTf)_4$	0.025	413	γ-bulac.	0.7	97.6	0.7	1.6

[1)] based on 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate [2)] bath temperature

EC : ethylene carbonate; Buac: n-butyl acetate; γ-bulac : γ-butyrolactone

A : 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate (and minor amounts of isomers)

B : (all-rac)-α-tocopheryl acetate

C : (all-rac)-α-tocopherol D : "phytadienes"

Claims

1. A process for the preparation of α-tocopheryl acetate which comprises reacting 2,3,6-trimethylhydroquinone-1-acetate with isophytol or phytol in the presence of a catalyst of the formula $M(RSO_3)_n$, wherein M is a silver, gallium or rare earth metal cation, n is the valence of the cation M, and R is fluoro, fluorinated lower alkyl or fluorinated aryl, in an aprotic organic solvent, and, if required, cyclizing any 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate or an isomer thereof obtained as an intermediate reaction product, to produce α-tocopheryl acetate.

2. A process as in claim 1 wherein in the catalyst M is Ag^{+}, Cu^{+}, Ga^{3+}, Sc^{3+}, Lu^{3+}, Hf^{4+}, Ho^{3+}, Tm^{3+}, or Yb^{3+}.

3. A process as in claim 1 wherein in the catalyst M is Sc^{3+}.

4. A process as in any one of claims 1-3 wherein in the catalyst R is trifluoromethyl.

5. A process as in any one of claims 1-4 wherein the catalyst is used in an amount of from about 0.001 mol-% to about 1 mol-% based on isophytol or phytol.

6. A process as in any one of claims 1-5 wherein the solvent is a two-phase solvent system.

7. A process as in claim 6 wherein one phase of the two-phase solvent system is ethylene carbonate or propylene carbonate or a mixture thereof, and the other phase is hexane, heptane, or octane.

8. A process as in claim 6 wherein the solvent system is ethylene carbonate/heptane.

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